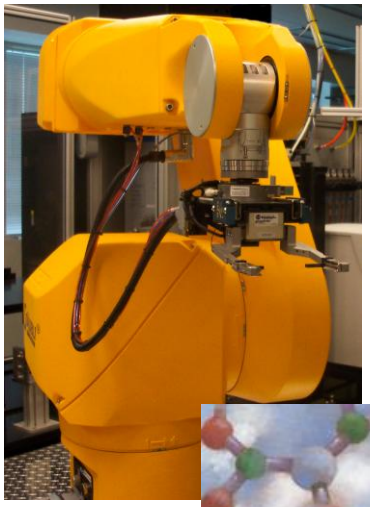
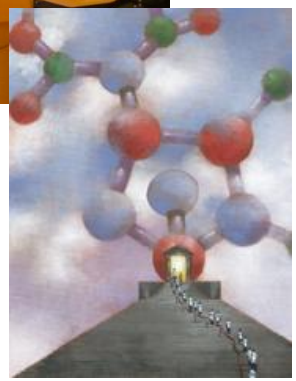
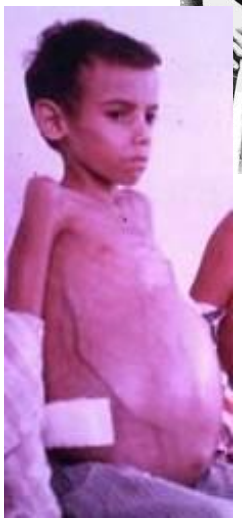




# The Therapeutics for Rare and Neglected Diseases (TRND) Program

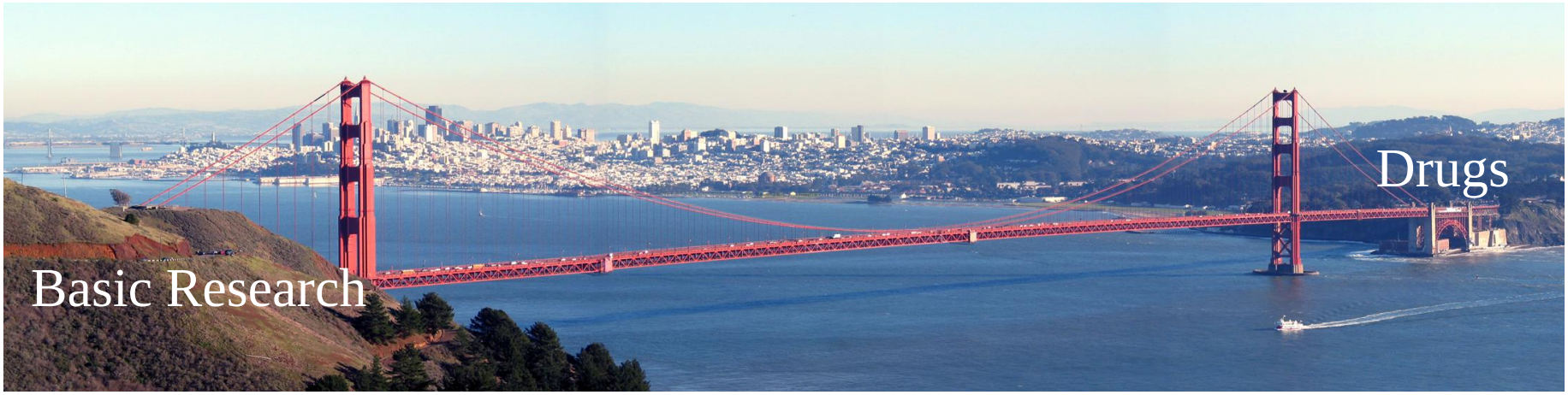



Christopher P. Austin, M.D.
Director, NIH Chemical Genomics Center
Senior Advisor to the NHGRI Director for Translational Research
National Institutes of Health

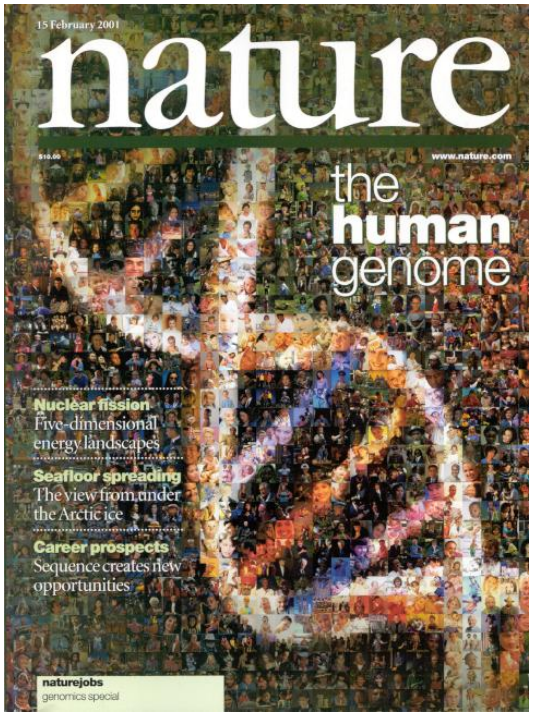
*99th Meeting of the Advisory Committee to the Director*
*National Institutes of Health*
*December 4, 2009*

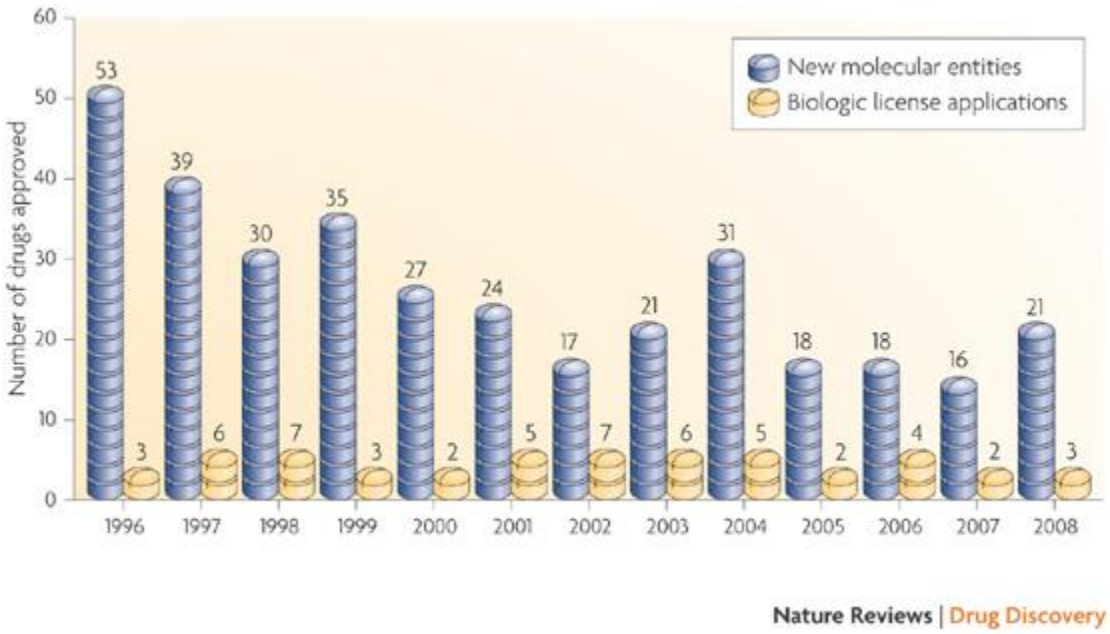
# The Problem


# The Opportunity



# The best of times, the worst of times




How to translate the genome into biological insights and therapeutics?

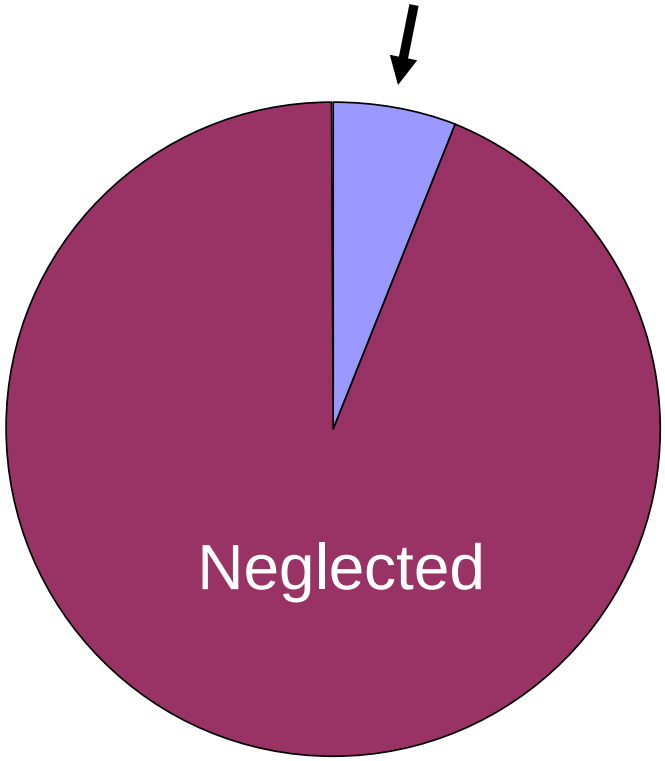
# The Problem of Rare and Neglected Diseases

- ~7,000 diseases affect humankind
- Only a very small fraction of diseases support commercial development of therapeutic agents
- Two types of neglected diseases:
  - Low prevalence, i.e., "rare"
    - Prevalence <200,000 in USA
    - There are >6000 rare (orphan) diseases
    - Cumulative prevalence in U.S. ~ 25 – 30 million
    - Most are single gene diseases; e.g., cystic fibrosis, Huntington disease, sickle cell disease, Tay-Sachs
    - Approximately 200 have any pharmacotherapy available from the 340 products approved by FDA
  - High prevalence but "neglected"
    - Occur chiefly among impoverished and marginalized populations in developing nations who are unable to afford treatments
    - Most are infectious diseases, e.g., malaria, schistosomiasis, leishmaniasis, trypanosomiasis

# Only a small % of diseases and genome-encoded targets are being addressed for drug development

**Current drug targets:**

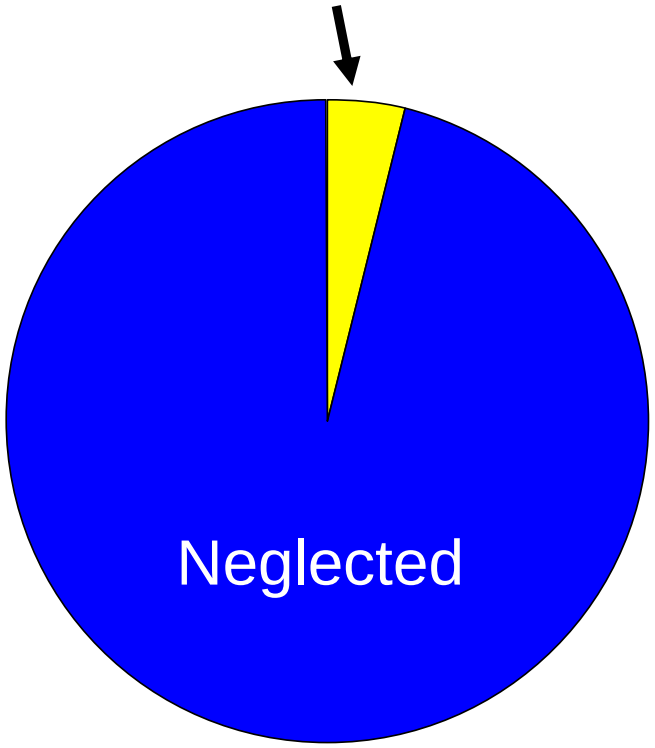
Well understood proteins




**Human Genome**

**Current diseases:**

Prevalent diseases that affect developed world

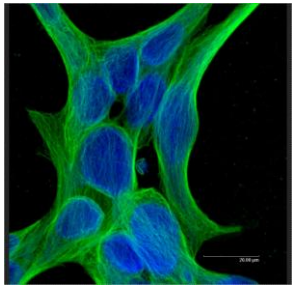


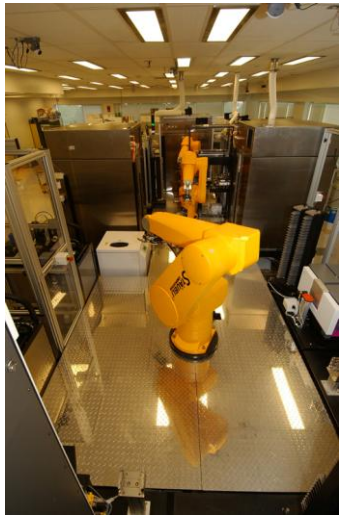

**Human Diseases**

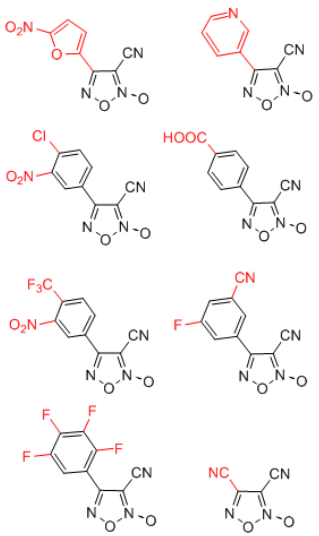
NIH Chemical Genomics Center

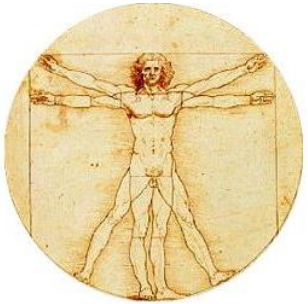
# Steps in the drug development process

Identify target → Create testing system (aka, “assay”) → Test >100,000 chemicals for activity on target → Make modifications to active chemicals to make suitable for human use → Test in animals for safety, effectiveness → Test in humans for safety, effectiveness



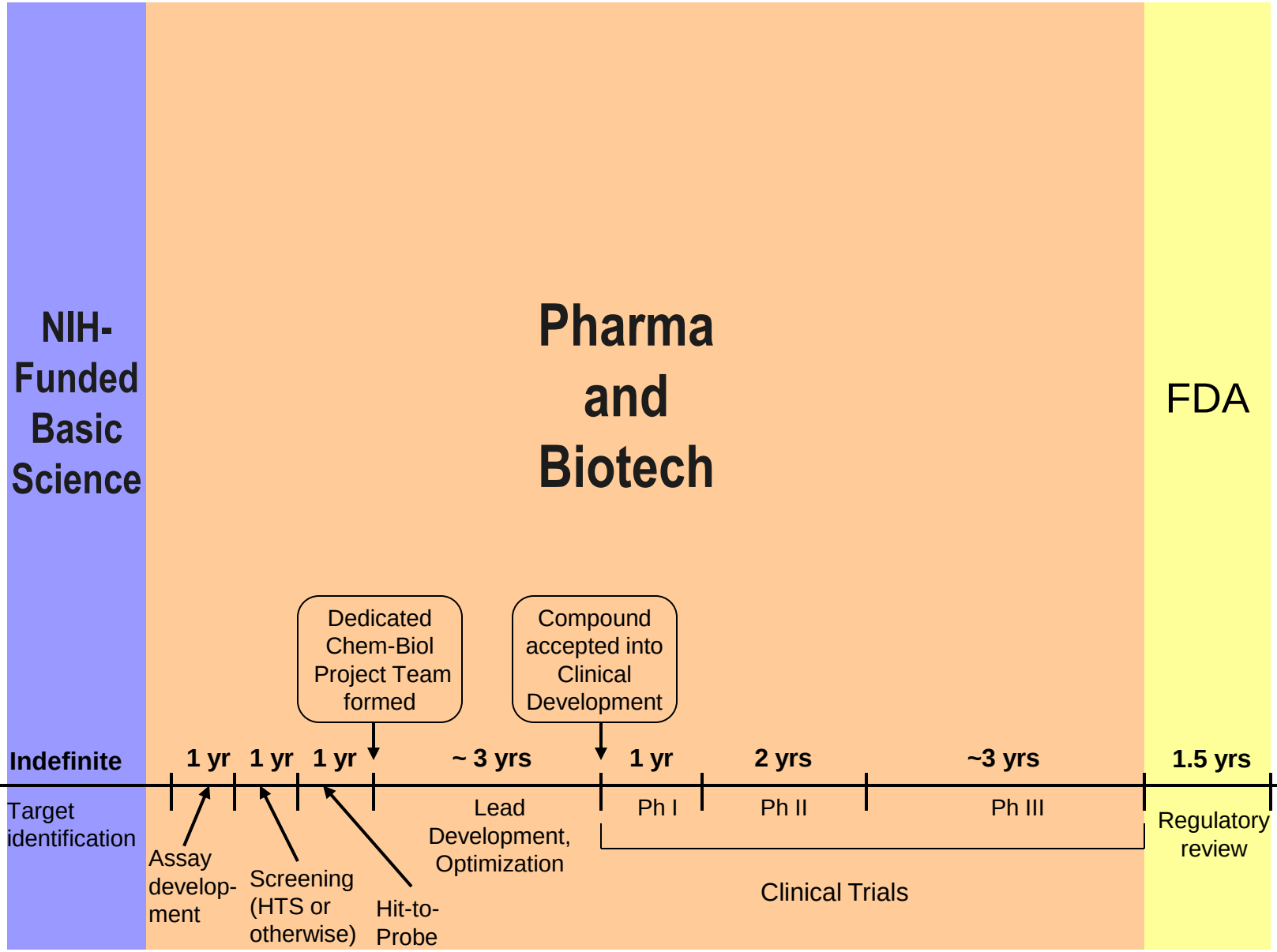






NIH Chemical Genomics Center

# Conventional roles of NIH and biopharma in drug development



NIH Roadmap ACCELERATING MEDICAL DISCOVERY TO IMPROVE HEALTH

Home Page

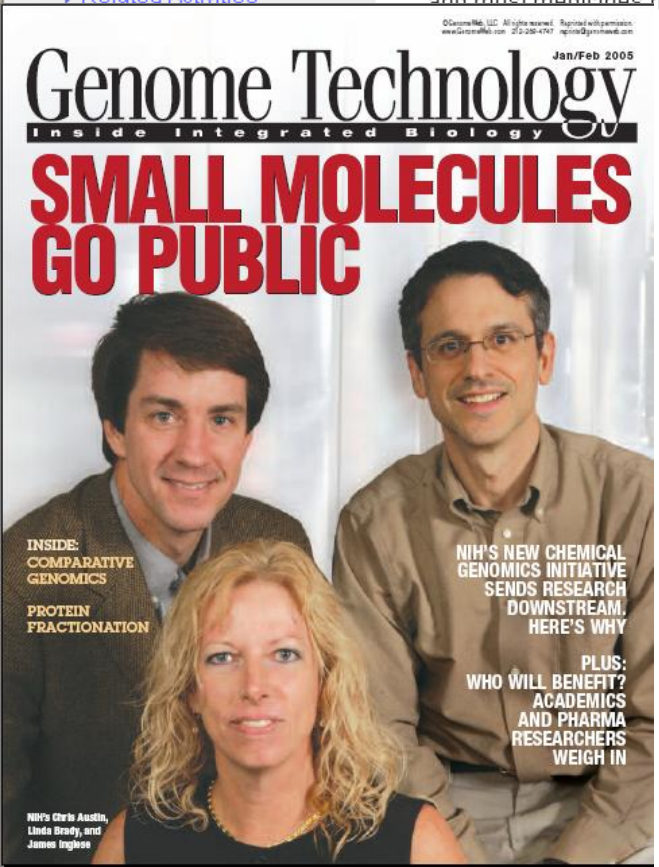
**Molecular Libraries and Imaging**

- Overview
- Implementation Group Members
- Funding Opportunities
- Funded Research
- Related Activities

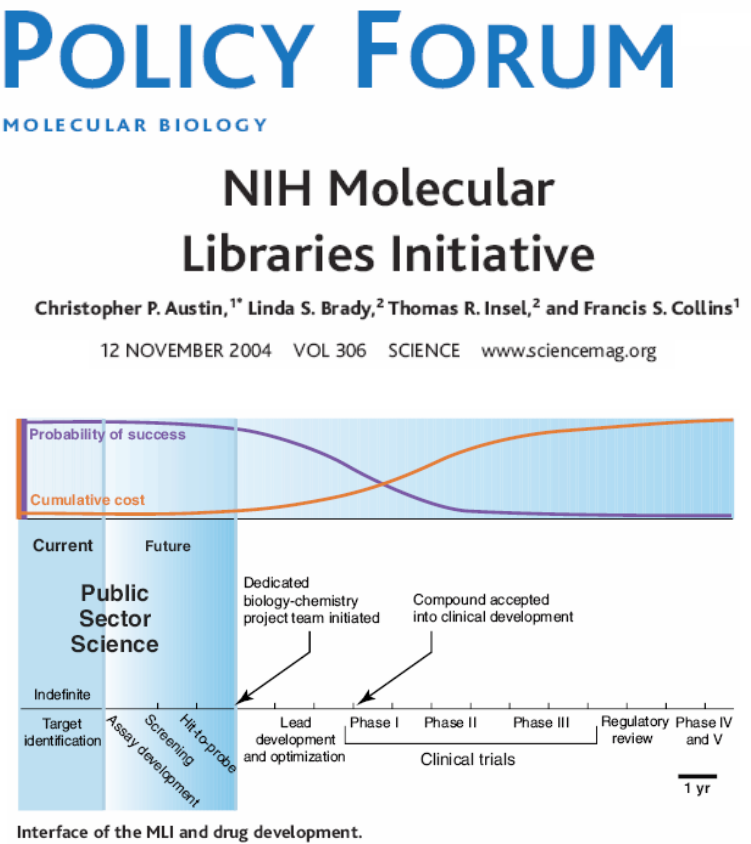
# Molecular Libraries and Imaging

## OVERVIEW

Small molecules, often with molecular weights of 500 or below, have proven to be extremely important to researchers to explore function at the molecular, cellular, and in vivo level. Such molecules have also been proven to be valuable for treating diseases, and most medicines marketed today are from this class.




***"…To empower the research community to use small molecule compounds in their research, whether as tools to perturb genes and pathways, or as starting points to the development of new therapeutics for human disease."***




Interface of the MLI and drug development.

# http://mli.nih.gov




**Access MLPCN Resources**

- MLPCN Centers
- Center Capabilities
- Access to Technical Assistance (MLPCN)
- Documents & Definitions

**User Login Required**

- MLP
- CARS
- CARS Training
- Assay Wiki
- Assay Annotation

**Search**

type, hit enter

## Access MLPCN Resources

**SubMenus:** MLPCN Centers | Center Capabilities | Technical Assistance | Documents & Definitions

The MLPCN resource can be accessed by any member of the scientific community in a number of ways,

If you **already have an HTS-ready assay** (in 96, 384, 1536-well plate or flow cytometry), then you can:

- Obtain technical assistance in developing a high throughput screening (HTS) plan by clicking here
- Apply through R03 Assay Implementation for peer review organized by CSR

If you have a **potentially HTS-compatible** assay (in test tube or 96-well plate)

- Obtain technical assistance in developing a high throughput screening (HTS) plan by clicking here
- Apply through R21 Assay Development for peer review organized by CSR

If you are a PI of an **existing assay grant (R21, R01 etc)** you can

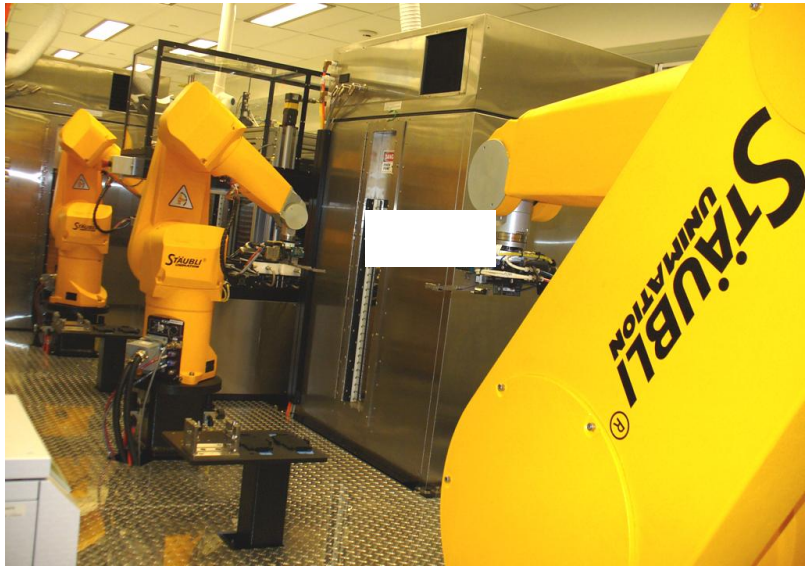
- Obtain technical assistance in developing a high throughput screening (HTS) plan by clicking here.
- Fast Track Entry of Assay Projects Apply for Fast Track entry to MLPCN click: Fast Track Entry Request.

If you wish to **submit compounds to the Molecular Libraries Small Molecule Repository** you can:

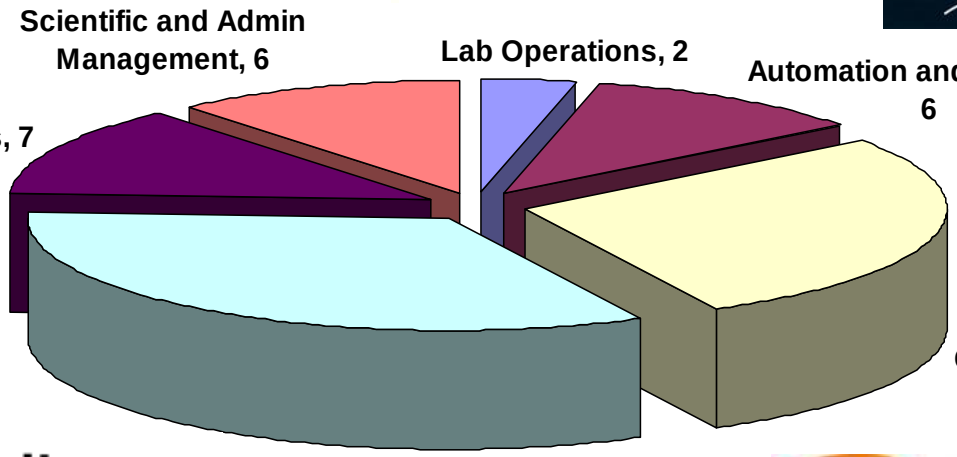
- Find guidance for compound submission here
- Contact Jamie Driscoll

# NIH Chemical Genomics Center

- Founded as part of Roadmap
- 75 scientists
- > 100 collaborations with investigators worldwide
  - 75% NIH extramural
  - 15% Foundations, Research Consortia, Pharma/Biotech
  - 10% NIH intramural
- Focus on novel targets, rare/neglected diseases
- Produces
  - chemical probes/leads
  - new paradigms for assay development, screening, informatics, chemistry



# NCGC Staff




NIH Chemical Genomics Center

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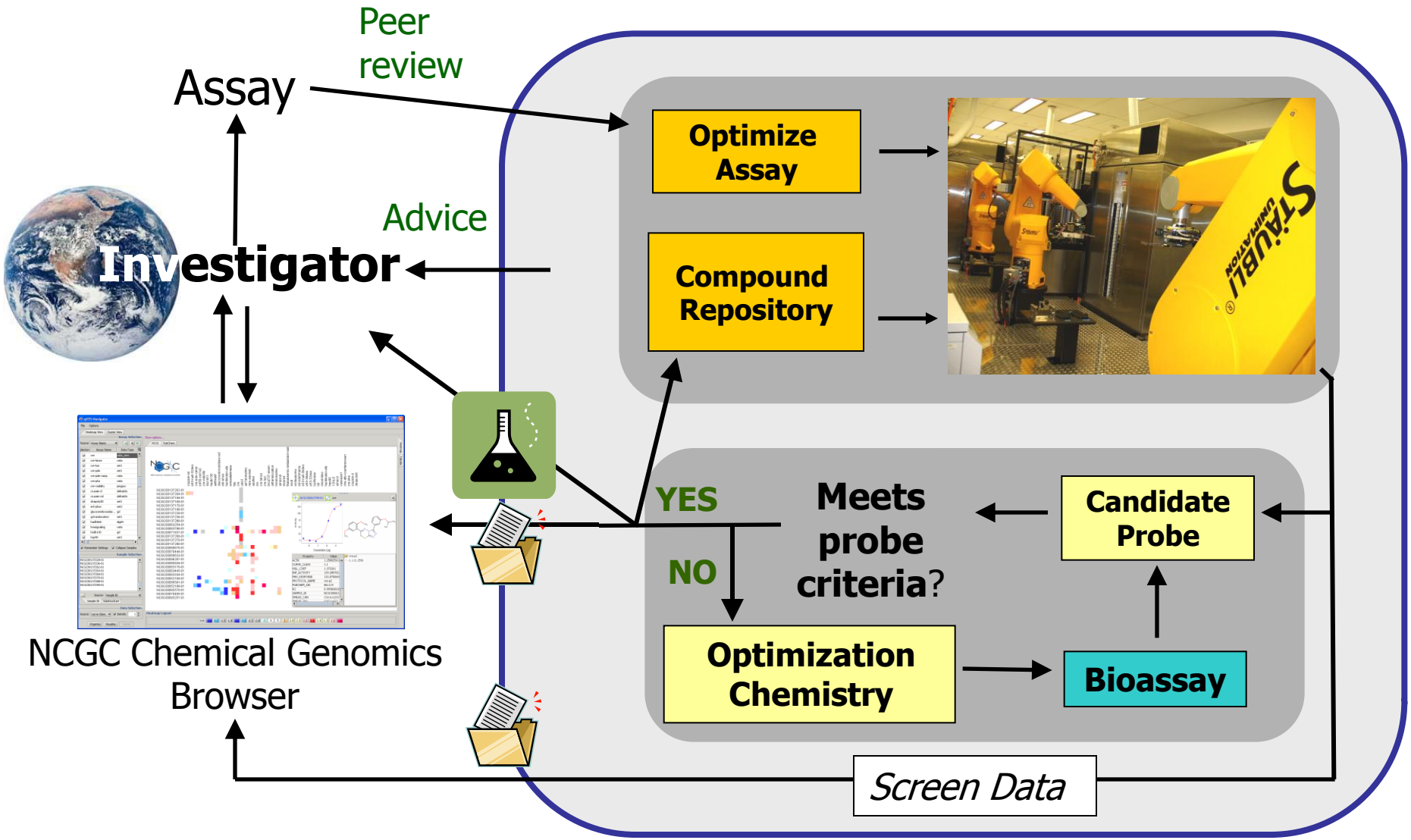
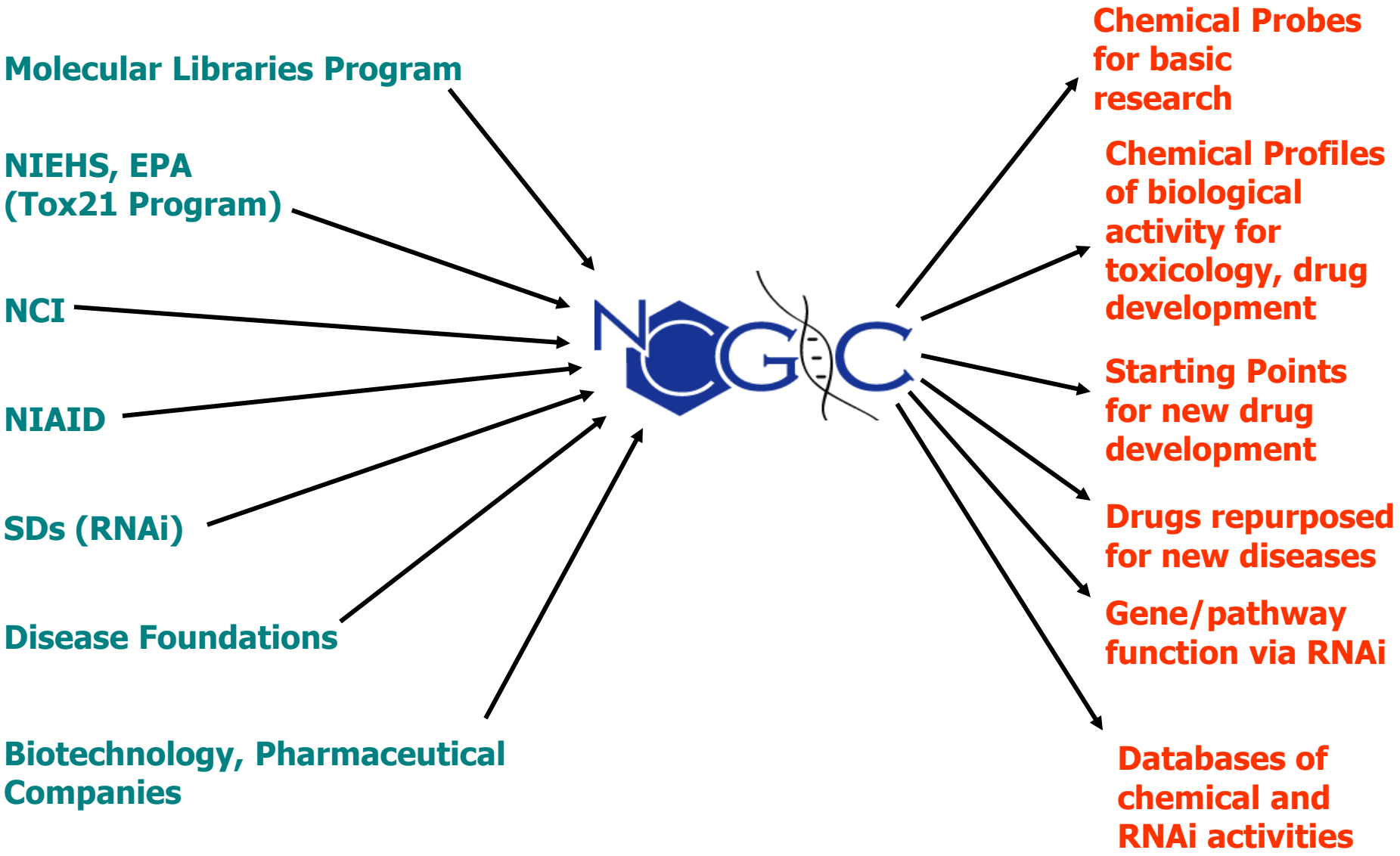
# NCGC Operation



# The NCGC: Enabling All ICs' Missions

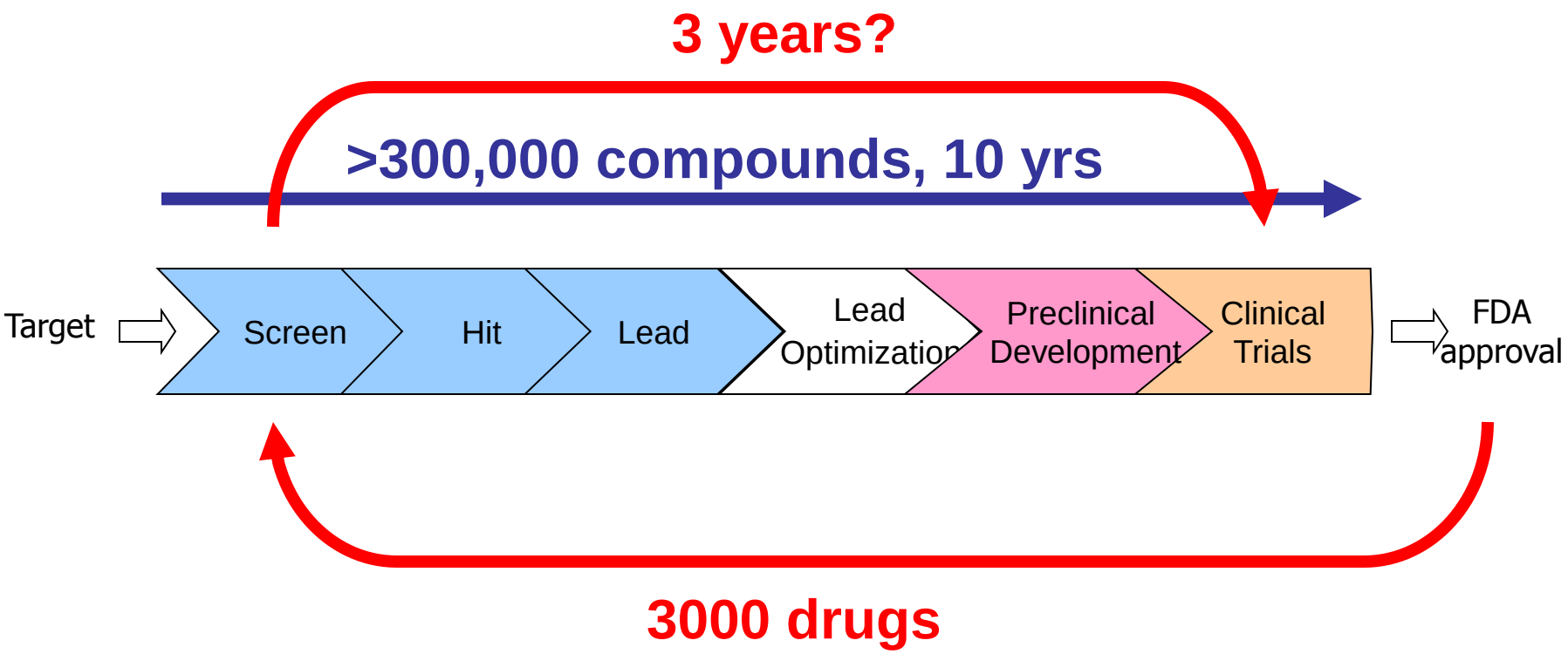


# Rare/neglected disease projects at NCGC

- Ataxia-telangiectasia
- Beta-thalassemia
- Charcot-Marie-Tooth
- Chordoma
- Chronic lymphocytic leukemia
- Gaucher disease
- Huntington's disease
- Leishmaniasis
- Lymphangioleiomyomatosis
- Malaria
- Myotonic dystrophy
- Niemann-Pick C
- Progeria
- Schistosomiasis
- Spinal muscular atrophy
- Trypanosomiasis

NCGC
NIH Chemical Genomics Center

# Two approaches to therapeutics for rare and neglected diseases



# NCGC Pharmaceutical Collection

## *Status May 2009*

| *Drug Source* | *In house* | *Need to procure* | *Total* |
|---|---|---|---|
| ***US FDA*** | 1531 | 178 | 1709 |
| ***UK/EU/Canada/Japan*** | 815 | 200 | 1015 |
| ***INN*** | 745 | 3591 | 4336 |
| ***Total Approved*** | 2346 | 378 | 2724 |
| ***Total*** | 3091 | 3969 | 7060 |

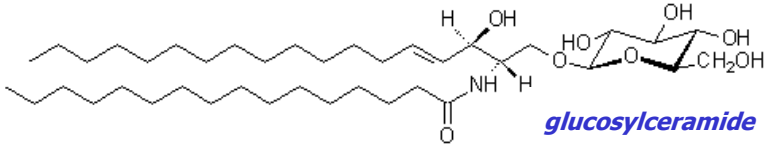
- Informatics sources for NPC
  - US FDA: Orange Book, OTC, NDC, Green Book, Drugs at FDA
  - Britain NHS
  - EMEA
  - Health Canada
  - Japan NHI
- Physical sources for NPC
  - Procurement from >20 suppliers worldwide
  - In-house purification of APIs from marketed forms
  - Synthesis

NIH Chemical Genomics Center

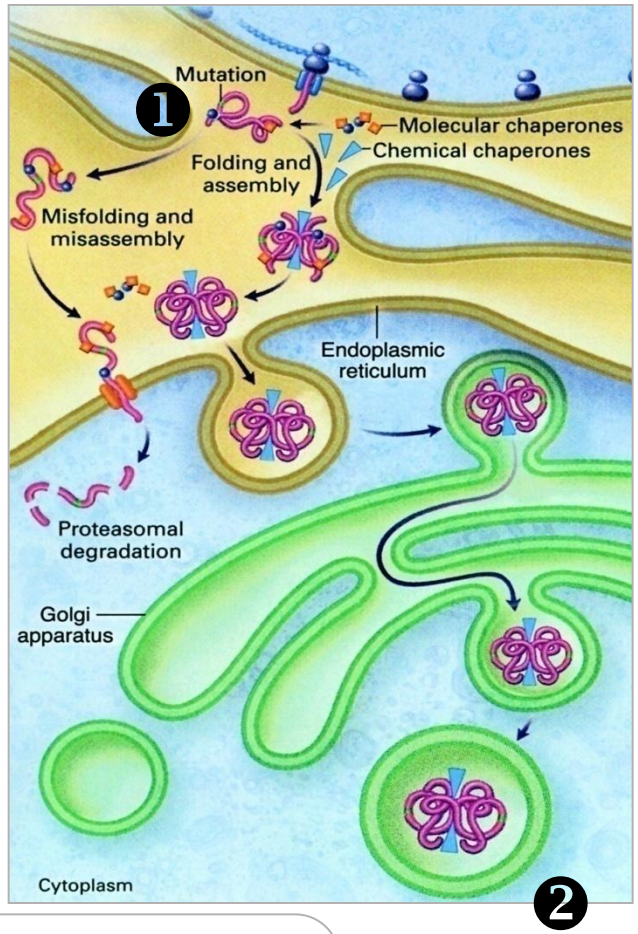
# Ameliorating the Defect in Gaucher's Disease

*NCGC Collaboration with Ellen Sidransky, NHGRI*

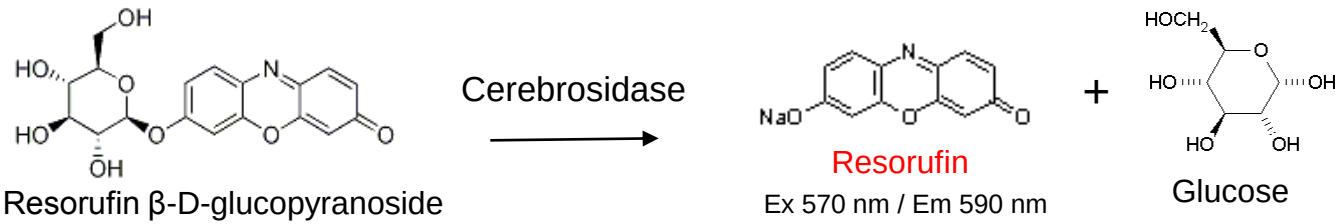
- Gaucher's Disease
  - Rare disease caused by mutations in enzyme glucocerebrosidase (GCS)




  - Current treatment: enzyme replacement
    - Limited efficacy, no BBB penetration, expensive
- Many mutations are missense, leading to trafficking defect
  - Pharmacological chaperones a therapeutic possibility




Fluorogenic substrate assay:




Resorufin β-D-glucopyranoside

NIH Chemical Genomics Center

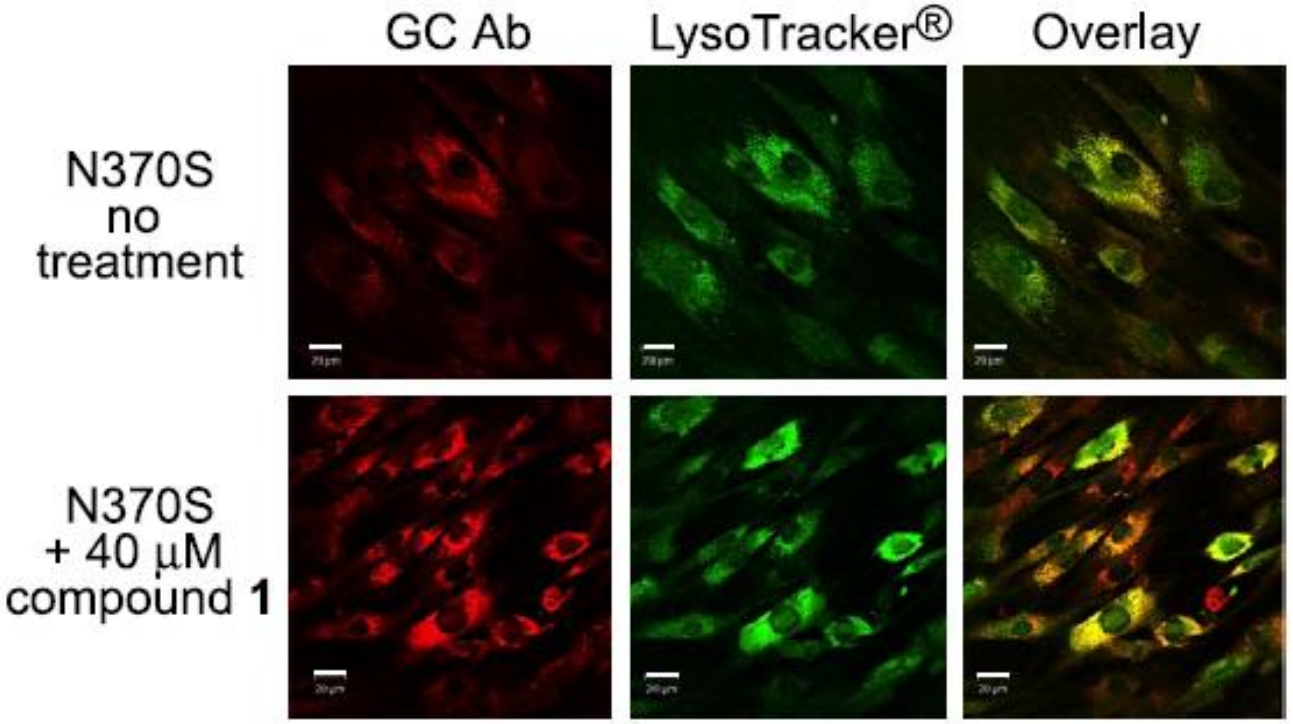
# Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease

**Wei Zheng*, Janak Padia*, Daniel J. Urban†, Ajit Jadhav*, Ozlem Goker-Alpan†, Anton Simeonov*, Ehud Goldin†, Douglas Auld*, Mary E. LaMarca†, James Inglese*, Christopher P. Austin*‡, and Ellen Sidransky†‡**

*NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, 9800 Medical Center Drive, MSC 3370, Bethesda, MD 20892-3370; and †Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Building 35 Rm1A213, 35 Convent Drive, Bethesda, MD 20892-3708

Communicated by Francis S. Collins, National Institutes of Health, Bethesda, MD, June 21, 2007 (received for review March 8, 2007)

13192–13197 | PNAS | August 7, 2007 | vol. 104 | no. 32




NIH Chemical Genomics Center

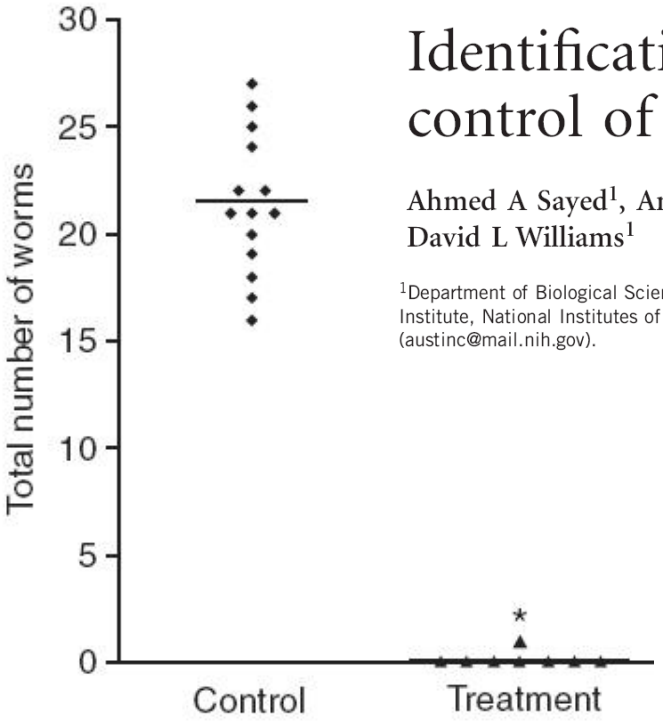
# Developing drugs for Schistosomiasis

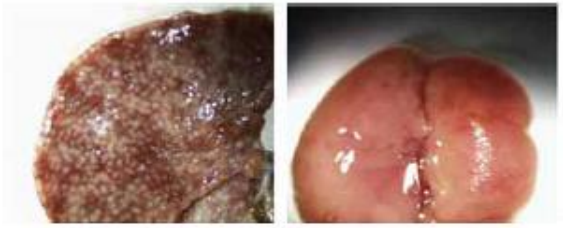
nature medicine

## Identification of oxadiazoles as new drug leads for the control of schistosomiasis

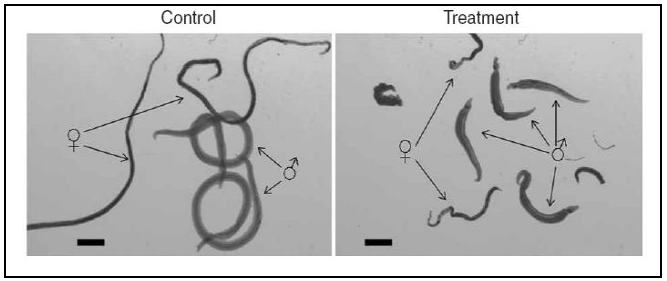
Ahmed A Sayed[1], Anton Simeonov[2], Craig J Thomas[2], James Inglese[2], Christopher P Austin[2] & David L Williams[1]

[1]Department of Biological Sciences, Illinois State University, Normal, Illinois 61790, USA. [2]NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-3370, USA. Correspondence should be addressed to D.L.W. (dlwilli@ilstu.edu) or C.P.A. (austinc@mail.nih.gov).



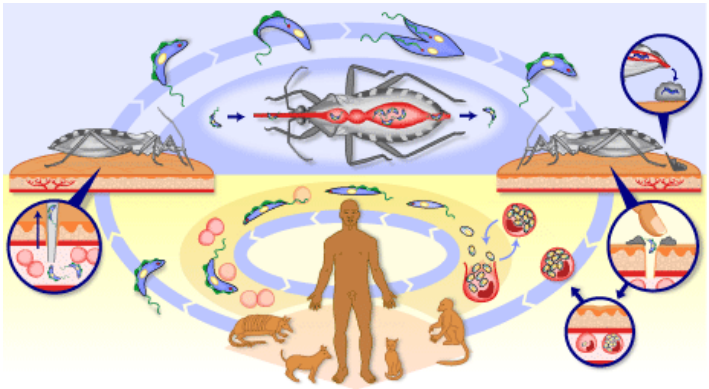
***Livers of treated mice***

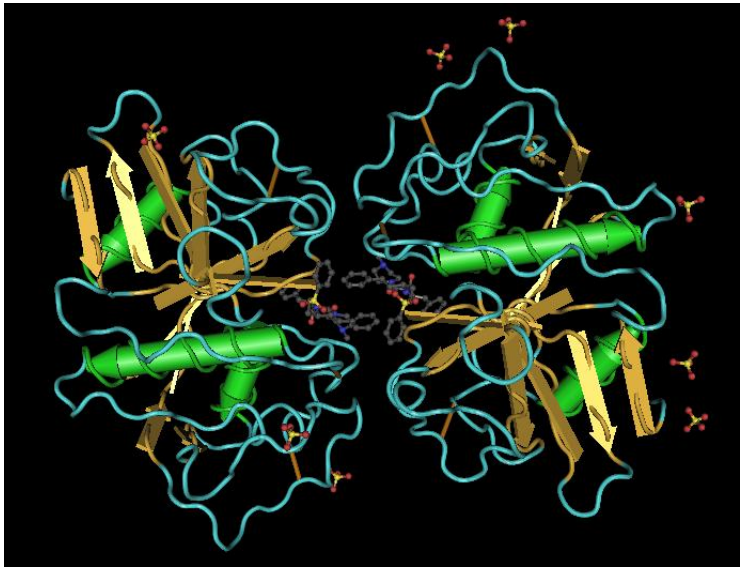



***Ex vivo worm killing***

# Cysteine protease inhibitors for Trypanosomiasis

## *Collaboration with Brian Shoichet and Jim McKerrow, UCSF*





Chagas disease: 16-18 million infected, annual mortality rate ~65,000; caused by the protozoan parasite *Trypanosoma cruzi*.

Typical disease carriers are bloodfeeding "Assassin bugs', which emerge at night to bite and suck blood. *T. cruz*i enters the human body through broken skin (from repeated scratching of the bitten area).

Current therapy: two drugs that only work during the acute phase.

Cruzain: major cysteine protease of T. cruzi, present during all stages of its lifecycle; essential for survival and replication of the parasite inside the host.

Journal of Medicinal Chemistry Article

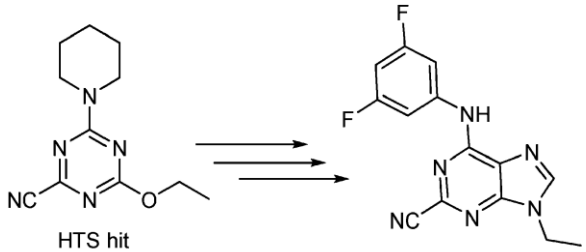
*J. Med. Chem.* **XXXX,** *XXX,* 000–000 **A**
DOI: 10.1021/jm901069a

# Identification and Optimization of Inhibitors of Trypanosomal Cysteine Proteases: Cruzain, Rhodesain, and TbCatB

Bryan T. Mott,[‡,▽] Rafaela S. Ferreira,[§,#,⊥,▽] Anton Simeonov,[‡] Ajit Jadhav,[‡] Kenny Kean-Hooi Ang,[∥] William Leister,[‡] Min Shen,[‡] Julia T. Silveira,[‡] Patricia S. Doyle,[#] Michelle R. Arkin,[∥] James H. McKerrow,[#] James Inglese,[‡] Christopher P. Austin,[‡] Craig J. Thomas,[‡] Brian K. Shoichet,[§] and David J. Maloney*[,‡]

[‡]*NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, 9800 Medical Center Drive, MSC 3370 Bethesda, Maryland, 20892-3370,* [§]*Department of Pharmaceutical Chemistry,* [∥]*Small Molecule Discovery Center,* [⊥]*Graduate Program in Chemistry and Chemical Biology and* [#]*Sandler Center for Basic Research in Parasitic Diseases, University of California San Francisco, 1700 Fourth Street, San Francisco, California, 94158-2550.* [▽]*Both of these authors contributed equally to this work.*

Journal of Medicinal Chemistry Article

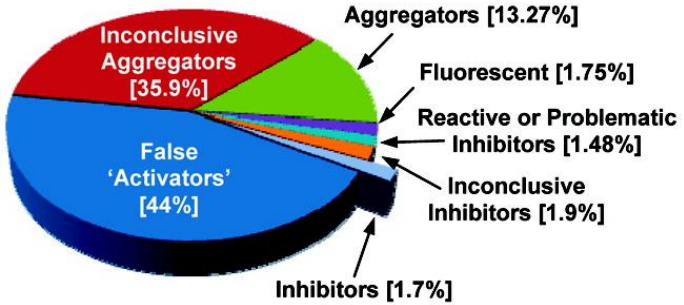



*J. Med. Chem.* **XXXX,** *XXX,* 000–000 **A**
DOI: 10.1021/jm901070c

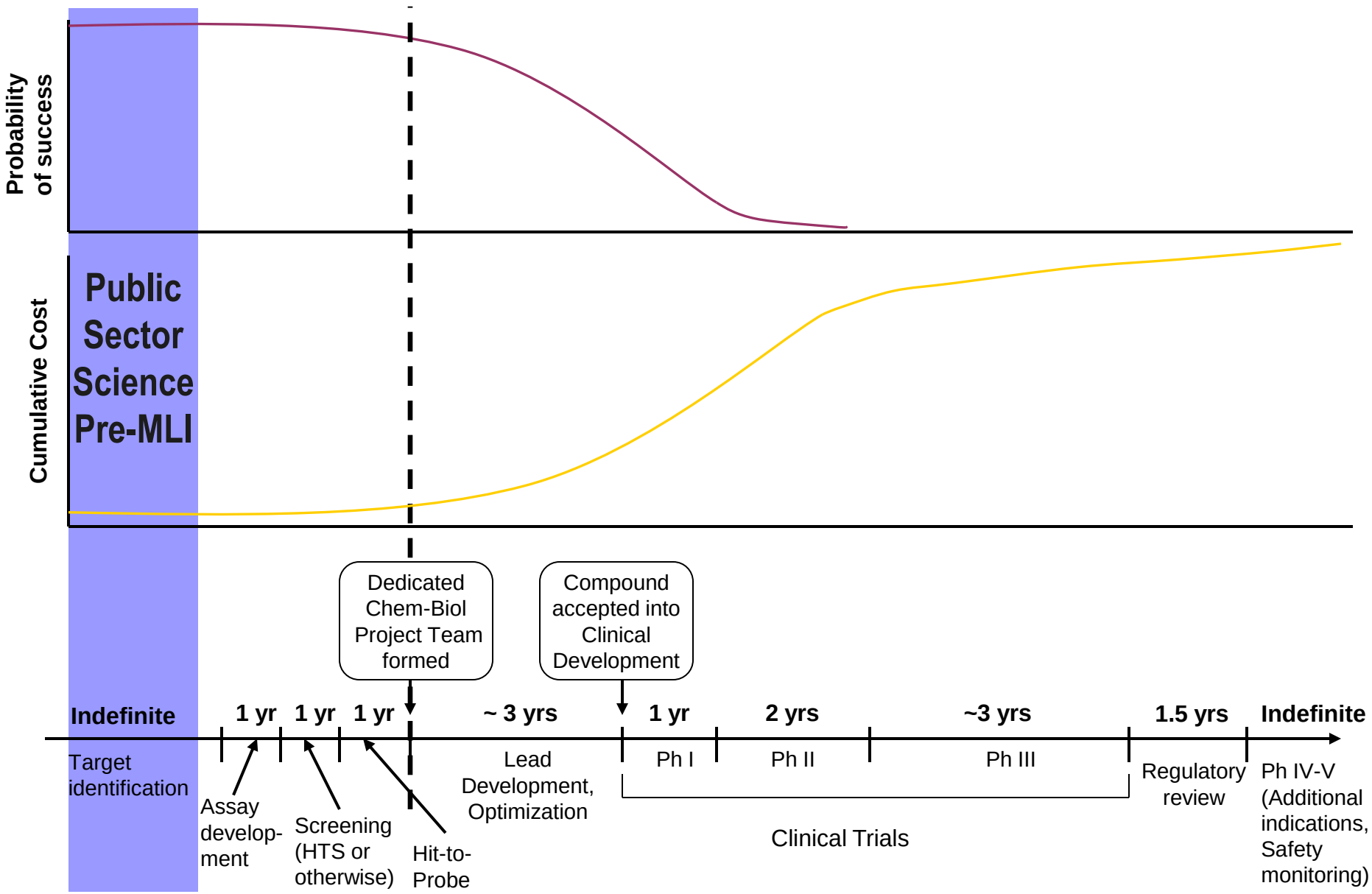
# Quantitative Analyses of Aggregation, Autofluorescence, and Reactivity Artifacts in a Screen for Inhibitors of a Thiol Protease

Ajit Jadhav,[†,§] Rafaela S. Ferreira,[‡,§] Carleen Klumpp,[†] Bryan T. Mott,[†] Christopher P. Austin,[†] James Inglese,[†] Craig J. Thomas,[†] David J. Maloney,[†] Brian K. Shoichet,*[,‡] and Anton Simeonov*[,†]

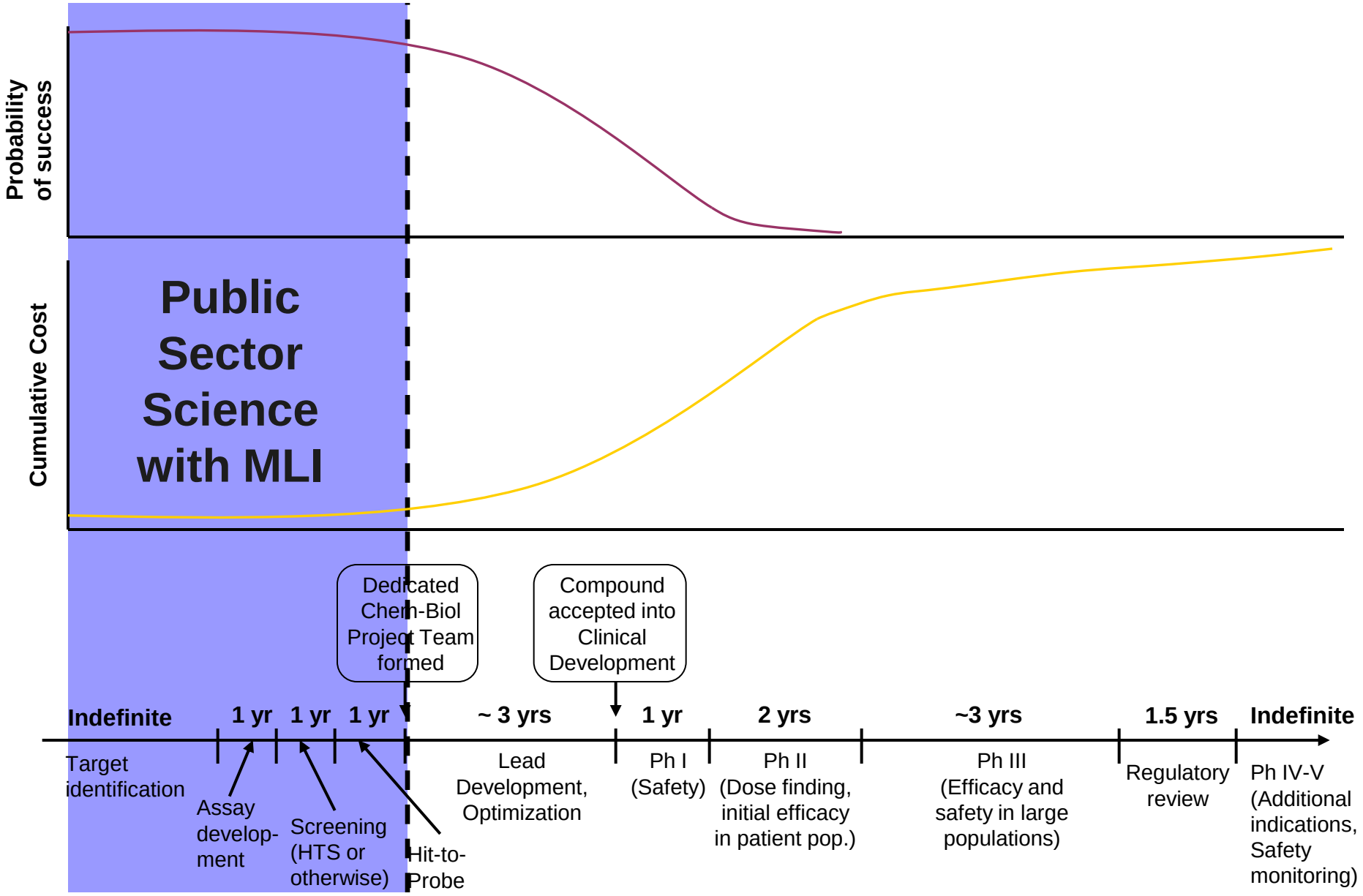
[†]*NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-3370, and* [‡]*Department of Pharmaceutical Chemistry, University of California San Francisco, 1700 Fourth Street, San Francisco, California, 94158-2550.* [§]*Joint first authors.*



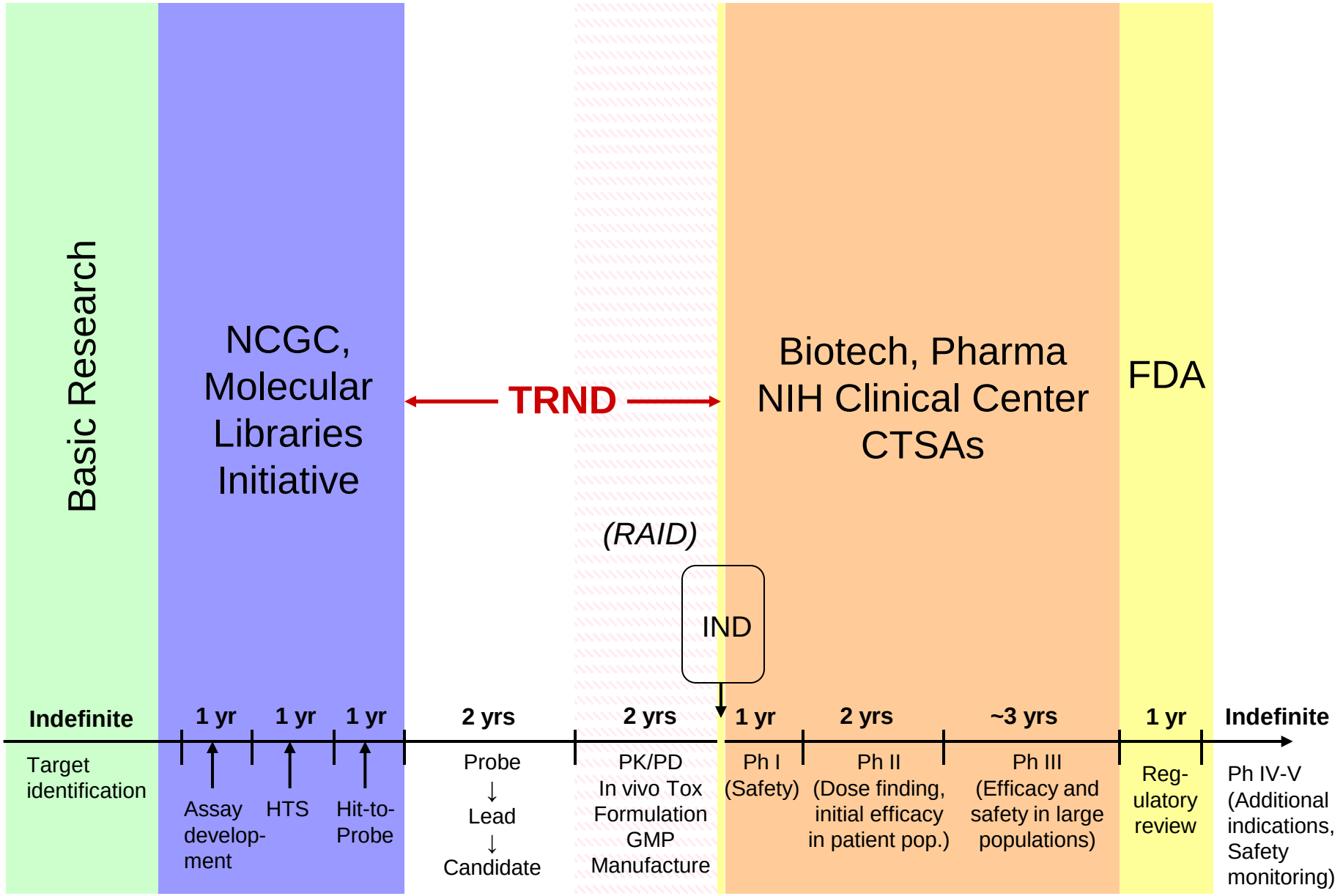
# Probes are just the start of drug development



# Probes are just the start of drug development



# TRND program will bring compounds to point of clinical testing/commercial adoption



U.S. Department of Health and Human Services
NIH News
National Institutes of Health

**Office of Rare Diseases Research**
www.genome.gov

**NIH Chemical Genomics Center**
www.ncgc.gov

**National Human Genome Research Institute**
www.genome.gov

# NIH Announces New Program to Develop Therapeutics for Rare and Neglected Diseases

**Bethesda, Md.**, Wed., May 20, 2009 — The National Institutes of Health is launching the first integrated, drug development pipeline to produce new treatments for rare and neglected diseases. The $24 million program jumpstarts a trans-NIH initiative called the Therapeutics for Rare and Neglected Diseases program, or TRND.

The program,, is unusual because TRND creates a drug development pipeline within the NIH and is specifically intended to stimulate research collaborations with academic scientists working on rare illnesses. The NIH Office of Rare Diseases Research (ORDR) will oversee the program, and TRND's laboratory operations will be administered by the National Human Genome Research Institute (NHGRI), which also operates the NIH Chemical Genomics Center (NCGC), a principal collaborator in TRND. Other NIH components will also participate in the initiative.

A rare disease is one that affects fewer than 200,000 Americans. NIH estimates that, in total, more than 6,800 rare diseases afflict more than 25 million Americans. However, effective pharmacologic treatments exist for only about 200 of these illnesses. Many neglected diseases also lack treatments. Unlike rare diseases, however, neglected diseases may be quite common in some parts of the world, especially in developing countries where people cannot afford expensive treatments. Private companies seldom pursue new therapies for these types of illnesses because of high costs and failure rates and the low likelihood of recovering investments or making a profit.

"NIH is eager to begin the work to find solutions for millions of our fellow citizens faced with rare or neglected illnesses," said NIH Acting Director Raynard S. Kington, M.D., Ph.D. "The federal government may be the only institution that can take the financial risks needed to jumpstart the development of treatments for these diseases, and NIH clearly has the scientific capability to do the work."

## Developing Drugs

The drug development process is complicated and expensive. Studies suggest that it currently takes more than a dozen years and hundreds of millions of dollars to take a potential drug from discovery to the marketplace. And the failure rate is high.

"This initiative is really good news for patients with rare or neglected diseases," said ORDR Director Stephen C. Groft, Pharm.D. "While Congress has previously taken important steps to help these patients, such as providing incentives for drug companies under the Orphan Drug Act, this is the first time NIH is providing support for specific, preclinical research and product development known to be major barriers preventing potential therapies from entering into clinical trials for rare or neglected disorders. While we do not underestimate the difficulty of developing treatments for people with these illnesses, this program provides new hope to many people world-wide."

Typically, drug development begins when academic researchers studying the underlying cause of a disease discover a new molecular target or a chemical that may have a therapeutic effect. Too often, the process gets stuck at the point of discovery because few academic researchers can conduct all the types of studies needed to develop a new drug. If a pharmaceutical company with the resources to further the research does get involved, substantial preclinical work begins with efforts to optimize the chemistry of the potential drug. This involves an iterative series of chemical modifications and tests in progressively more complex systems - from cell cultures to animal tests - to refine the potential medicine for use in people. Only if these stages are successful can a potential treatment move to clinical trials in patients.

Unfortunately, the success rate in this preclinical process is low, with 80 to 90 percent of projects failing in the preclinical phase and never making it to clinical trials. And the costs are high: it takes 2 to 4 years of work and $10 million, on average, to move a potential medicine though this preclinical process. Drug developers colloquially call this the "Valley of Death."

TRND will work closely with disease-specific experts on selected projects, leveraging both the in-house scientific capabilities needed to carry out much of the preclinical development work, and contracting out other parts, as scientific opportunities dictate. Its strategies will be similar to approaches taken by pharmaceutical and biotechnology companies, but TRND will be working on diseases mostly ignored by the private companies. Importantly, TRND will also devote some of its efforts to improving the drug development process itself, creating new approaches to make it faster and less expensive.

# The Scientific Issues

- The science is novel and extremely difficult, requiring:
  - Top scientific talent, to be recruited from the best pharmaceutical and biotechnology companies
  - Close daily coordination among many different disciplines that are physically co-located
  - A highly experimental approach with different models being tried simultaneously
  - Rapid shifting in priorities and deliverables depending on results
  - 20-person project teams will work for average of two years on each project with high failure rate
  - The successes frequently cannot be published due to IP

# TRND Operational Model

- Analogous to NCGC
- In-house laboratories with expertise in preclinical drug development will collaborate with external laboratories with expertise in disease/target
- Projects will be taken to phase needed for external organization to adopt for clinical development
- Projects will enter TRND at a variety of stages of development
- Distinguishing features
  - Disease agnostic, will look explicitly for cross-cutting mechanisms
  - Processes will be established to incorporate learning from each project to operationalize continuous improvement
  - *Science* of preclinical drug development
  - Reasons for successes and failures will be investigated and published

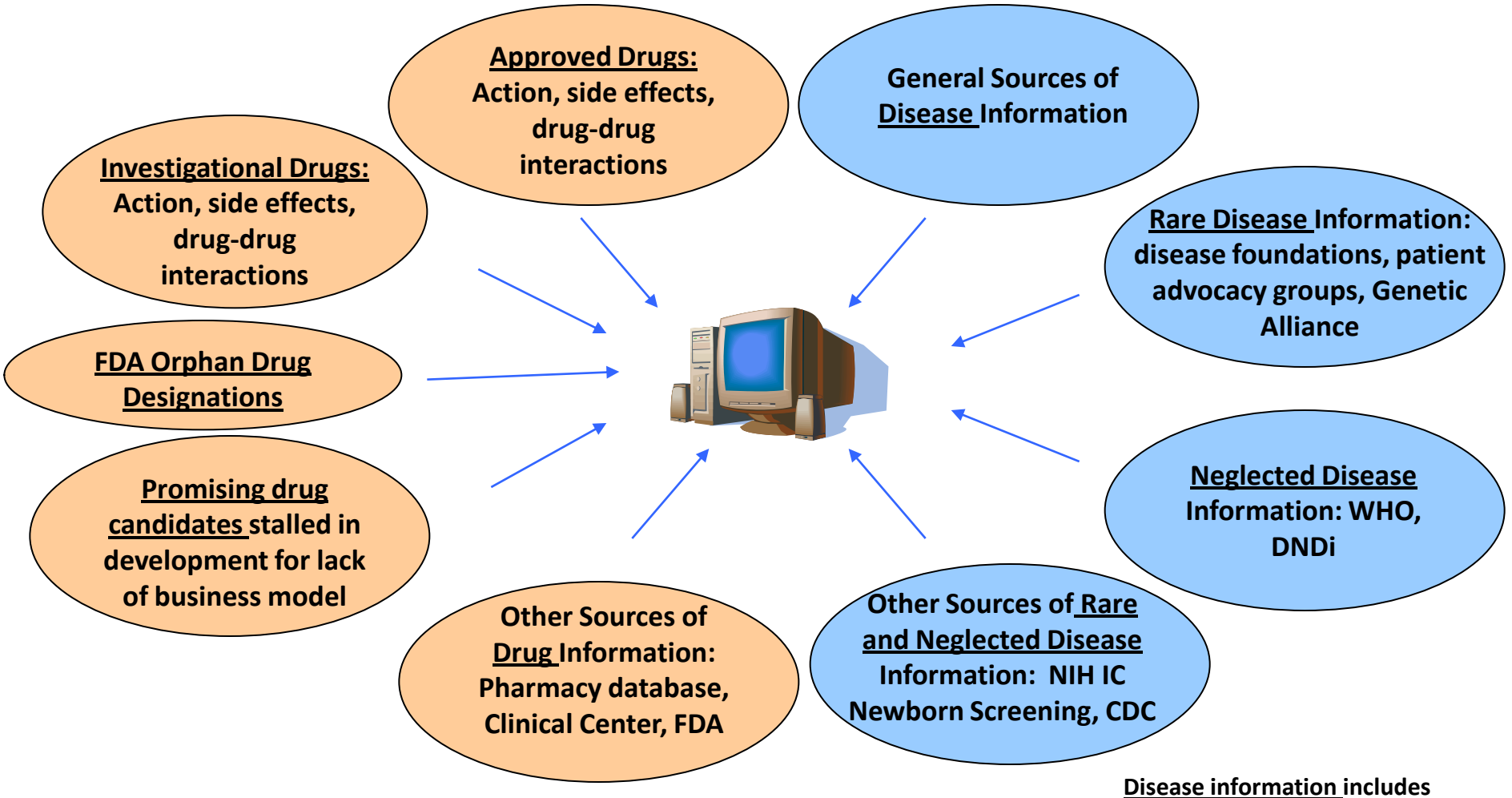
# TRND Science

- Administered by NHGRI (for now)
- Starting point: Chemical probe
- End point: Clinical candidate compound attractive for adoption by biotech/pharma
- Project-specific activities
  - Medicinal chemistry
  - *in vitro* efficacy, pharmacology, ADME, toxicology
  - *in vivo* drug metabolism, pharmacokinetics/pharmacodynamics, toxicology
  - Compound scale-up
- Technology/paradigm development
  - At least 20% of effort to improving success rates

# TRND is interacting with many different groups in planning activities

- US Government
  - NIH
    - Institutes and centers
      - Intramural including CC
      - Extramural
        - » funded researchers
        - » programs including CTSA, CTEP, RAID, NBS research network
    - Office of Tech Transfer
    - Office of General Counsel
  - FDA including CDER and OOPD
  - Centers for Disease Control and Prevention
  - Office of Science and Technology Policy
- Non-US government
  - Biotech and pharma companies
  - VC organizations
  - Rare disease foundations
  - Neglected disease organizations
  - Advocacy groups

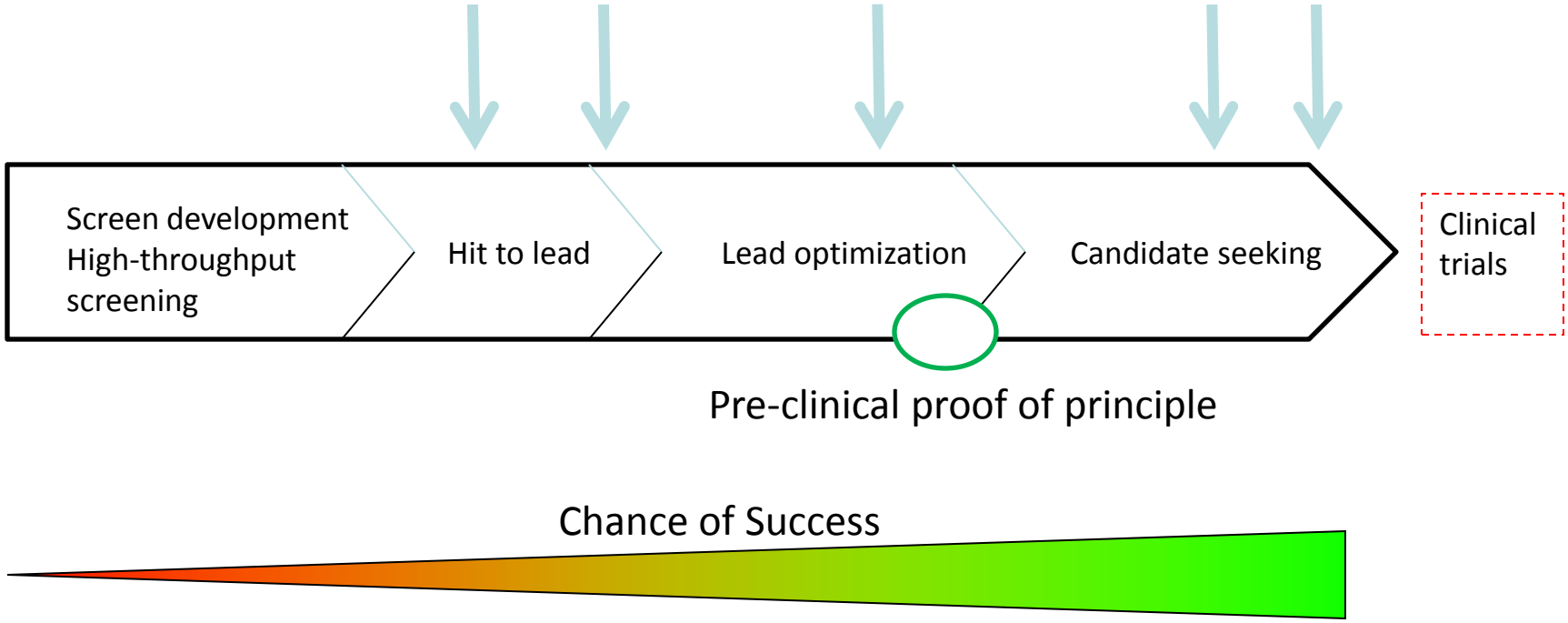
# Information Integration for TRND To Aid in Project Selection




Disease information includes symptoms, cause of death, pathogenesis, genetic information, etc.

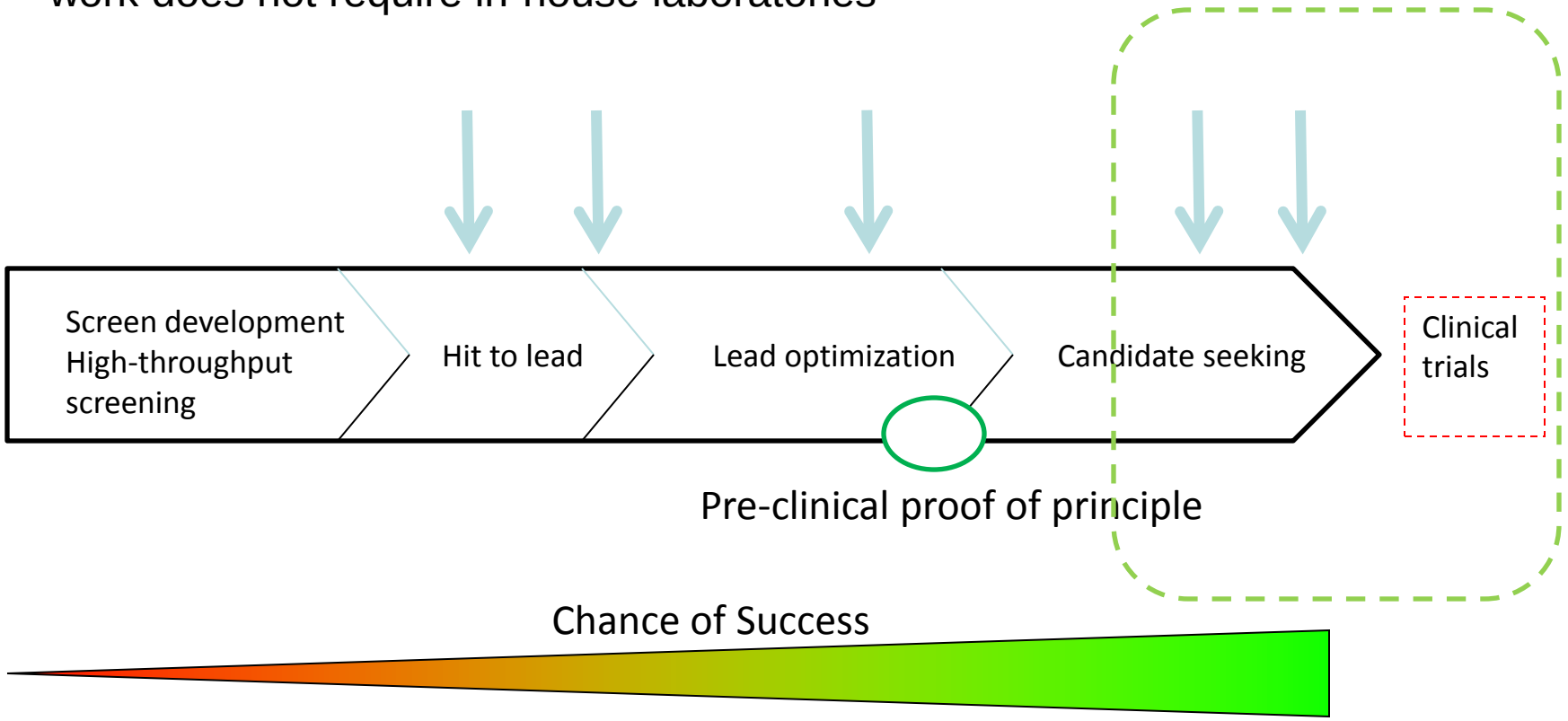
# Diversify Risk Based on Stage of Project

TRND will bring compounds into the pipeline at various stages of development



# TRND will concentrate early on projects closest to clinic

- compounds in industry that are stalled in development may be some of our best opportunities
- work does not require in-house laboratories



# TRND Operations

- Initial plan, assuming $24 M per year, is to work on approximately five projects per year
- The average project should take approximately two years
- Projects will be monitored closely for progress; those making insufficient headway will be culled quickly, to allow next project in pipeline to start as soon as possible
- Anticipated timeline
  - FY09: infrastructure
  - FY10: governance, hiring, research community outreach, 2-3 pilot projects to establish operational processes
  - FY11: solicitation of projects for adoption, 4-5 projects ongoing
  - FY12: fully operational

# TRND Governance *(working)*

- Centered at Office Of Rare Diseases Research
  - Takes advantage of ORDR's inherently pan-IC nature and long-standing relationships with rare disease community
- Active involvement and representation of ICs and community
  - ***Trans-NIH Staff Advisory Group***
    - Advise on operation
    - Help integrate TRND with related NIH efforts
  - ***Expert External Panel***
    - From academia, industry, and patient advocacy communities
    - Helps select projects
    - Assesses progress in an ongoing manner
    - Performs formal periodic assessments and recommendations regarding TRND

# TRND: Project Selection *(working)*

- Projects will be solicited from extramural and intramural researchers, foundations, and biotechs/pharmas
- Discussion ongoing about “bottom-up” or “top-down” project selection, or combination
- First-level review will be performed by the External Expert Panel
- Second-level review will be performed by the Trans-NIH Advisory Group
- ***Stay tuned***

# Questions